J. Clin. Chem. Clin. Biochem.
Vol. 26, 1988, pp. 509–519

Graphical Analysis of Laboratory Data in the Differential Diagnosis of Cholestasis: A Computer-Assisted Prospective Study

By *G. Börsch, J. Baier*

Medizinische Klinik der Ruhr-Universität Bochum am St. Josef-Hospital

M. Glocke, W. Nathusius

Abteilung für allgemeine Biometrie, Boehringer GmbH, Mannheim and

W. Gerhardt

Department of Clinical Chemistry, Lasarettet, Helsingborg, Sweden

(Received October 28, 1987/March 9, 1988)

Summary: Data on 15 laboratory analytes obtained in 145 prospectively investigated cholestatic patients with viral hepatitis, chronic intrahepatic cholestasis and extrahepatic biliary obstruction were submitted to a computer-based graphical evaluation using probabilistic test analysis. This revealed a marginal utility for alkaline phosphatase, γ-glutamyltransferase and the direct/total bilirubin ratio at specific cut-off points for the exclusion of extrahepatic cholestasis (PVneg 90%–100%). Aspartate aminotransferase and alanine aminotransferase values with cut-off points at 200 U/l and 300 U/l, respectively, were powerful discriminators between acute viral hepatitis and the other disease categories, while lactate dehydrogenase, erythrocyte sedimentation rate and the ratios γ-glutamyltransferase/alanine aminotransferase as well as total bilirubin/γ-glutamyltransferase were useful at specific cut-off points indicating the absence of this diagnosis (PVneg 92%–100%). An aspartate aminotransferase/alanine aminotransferase ratio above 1.5 and serum γ-globulin concentrations above 20 g/l strongly suggested cholestasis due to chronic parenchymal liver disease (PVpos 92% and 90%, respectively).

This graphical approach to laboratory data analysis enhances the understanding of the interrelations between cut-off points and sensitivity, specificity and predictive values and also of the influence of disease prevalence on disease prediction. It also adds to present knowledge by demonstrating the clinical relevance of several readily available, albeit rarely utilized diagnostic analytes.

Introduction

The differential diagnosis of cholestasis is based on a thorough clinical examination and on morphological studies of the hepatobiliary system by one or several imaging techniques, supplemented by an histological evaluation of liver tissues in selected patients. The initial clinical examination includes an analysis of the patient's history, of his or her physical symptoms, and of a set of biochemical variables. It aims at a preliminary assignment of each patient of either one of the two major diagnostic categories "intrahepatic" and "extrahepatic" cholestasis, which are listed with some further refinement in table 1.

Biochemical profiles are often useful for the reliable classification of patients into those suffering from acute parenchymal liver disease, with viral hepatitis

(VIR) as a hallmark (group B1 in tab. 1), or those suffering from chronic parenchymal liver disease (CHR) with cirrhosis, chronic hepatitis or chronic alcoholic liver disease as the main variants (group B2 in tab. 1). However, in cases with predominant bile stasis, it is widely accepted that clinical chemical parameters do not reliably differentiate between intrahepatic bile secretory failures or an extrahepatic biliary obstruction (EXT) (1). In this paper we have examined the usefulness of computer-assisted graphical analyses of laboratory data for the differential diagnosis of various hepatobiliary disease categories in prospectively evaluated cholestatic patients.

Patients and Methods

This study included 145 consecutive patients with cholestasis, which could be assigned to either one of four diagnostic categories as outlined in table 1, based on the results of imaging studies (hepatobiliary ultrasound, cholescintigraphy, or endoscopic retrograde cholangiography) and/or histologic or intraoperative findings, and also the clinical outcome. No attempt was made to differentiate between malignant or benign causes of extrahepatic cholestasis (EXT, tab. 1) by means of laboratory data. Criteria for cholestasis to be met before inclusion in this study were: bilirubin ≥ 2.0 mg/dl (34 µmol/l); γ-glutamyltransferase ≥ 100 U/l; alkaline phosphatase ≥ 300 U/l (at least two of these three conditions) or serum bilirubin ≥ 4 mg/dl (68 µmol/l). Morphological diagnostic proof either by direct cholangiography and/or histological and/or intraoperative or postmortem findings was obtained in 104/145 patients (72%).

Tab. 1. Patients and diagnostic categories

Group	Final diagnosis	n	♂/♀	Age (a)	SD (a)
A	Extrahepatic cholestasis (EXT)	64 (44%)			
A1	benign, mostly lithogenic cause	39	11/28	66.2	15.5
A2	obstruction by malignant cause	25	10/15	75.0	10.1
B	Intrahepatic cholestasis (INT)	81 (56%)			
B1	acute viral hepatitis (VIR)	23	7/16	47.2	18.8
B2	chronic intrahepatic cholestasis (CHR)	58	31/27	55.5	11.8

Tab. 2. Laboratory analytes and criteria for test analysis

Variables	Reference limit	Unit	Reduction of n	Reduction of values above	Method
Laboratory analytes					
Alkaline phosphatase	180	U/l	1/0	1200 U/l	Hitachi
γ-Glutamyltransferase	28	U/l	1/4	1000 U/l	Hitachi
Leucine aminopeptidase	32	U/l	0/3	165 U/l	Hitachi
Aspartate aminotransferase	20	U/l	0/0	1000 U/l	Hitachi
Alanine aminotransferase	20	U/l	8/0	1000 U/l	Hitachi
Lactate dehydrogenase	250	U/l	1/1	700 U/l	Hitachi
Cholinesterase	2000*	U/l	1/4	5000 U/l	Hitachi
Total serum bilirubin	1.0	mg/dl	0/0		Hitachi
Direct bilirubin			0/0		Hitachi
Erythrocyte sedimentation rate					
first hour	10	mm	0/7	100 mm	Westergren
second hour	20	mm	0/9	120 mm	Westergren
Immunoglobulin G	18	g/l	3/0	40 g/l	Laser
Immunoglobulin A	4.5	g/l	0/0		Laser
Immunoglobulin M	2.5	g/l	0/0		Laser
Total γ-globulin	10	g/l	3/0	40 g/l	CAF

Test criteria

Sensitivity:	fraction of test-positive "diseased" among all diseased
Specificity:	fraction of test-negative reference persons among all reference persons
PVpos:	(predictive value positive); "diseased" among all test-positive persons
PVneg:	(predictive value negative); reference persons among all test-negative persons
Youden index:	(sensitivity + specificity) − 100%

Values in the diseased/reference groups above the thresholds indicated in this table were reduced and included in the highest categories for this individual analyte. E. g., a value of 1600 U/l for alkaline phosphatase was included in the 1100 to 1200 U/l category. This served to reduce the number of test classes. (Abbreviations: Reference limit applies to upper normal limits except for cholinesterase*, where it denotes lower normal limit). "Hitachi" refers to Hitachi Automatic Analyzer 705, "Laser" to the Behring Laser Nephelometer-Analyzer.

A set of 15 laboratory analytes summarized in table 2 was routinely evaluated at the presentation of patients. In addition, several analytes were also used to compute ratios as indicated in table 3. These data were further evaluated by a graphical computer program (2). Briefly, this program produces double histograms presenting the distribution of laboratory data in both "diseased" and reference groups in the study. Each continual diagnostic variable was arbitrarily divided into 10 test classes. The probabilistic variables, sensitivity (sens), specificity (spec), predictive value positive (PVpos), predictive value negative (PVneg) and *Youden* index (tab. 2; see also l.c. (2, 3)) are superimposed on the histograms as functions of the cut-off laboratory values at any selected position. These discriminators basically serve to reduce the data to a two-class (binary) test equivalent to a 2 × 2 table, which is the prerequisite for computing the probabilistic test data for that specific cut-off point. In order to compare the predictive values of the tests, the data of each test were also recalculated to meet a "standard" prevalence of 50% "diseased". This computer program has been described in detail elsewhere (2). The various hypotheses graphically analysed in the present study are summarized in table 3. The original data are available on request from the first author.

Results

Extrahepatic versus intrahepatic cholestasis

A synopsis of all relevant diagnostic results from the graphical analyses is given in tables 4–6. When maximal efficiency as indicated by the highest *Youden* index was used as the cut-off point, none of the analytes investigated was of value for the basic differentiation between extrahepatic obstruction or intrahepatic cholestasis due to acute or chronic parenchymal liver disease. This likewise applied to the ratio of direct and total serum bilirubin (direct bilirubin/total bilirubin). The double histograms for alkaline phosphatase and direct bilirubin/total bilirubin are reproduced in figure 1 and figure 4. However, when selected discriminator positions for alkaline phospha-

Tab. 3. Study hypotheses

Analyte	"Diseased" group	Reference group	Target	Figure
Alkaline phosphatase	EXT	VIR + CHR	high	1
γ-Glutamyltransferase	EXT	VIR + CHR	high	2
Leucine aminopeptidase	EXT	VIR + CHR	high	3
Aspartate aminotransferase	VIR	EXT + CHR	high	6
Alanine aminotransferase	VIR	EXT + CHR	high	7
Lactate dehydrogenase	VIR	EXT + CHR	high	8
Cholinesterase	CHR	EXT + VIR	low	16
Erythrocyte sedimentation rate				
first hour	VIR	EXT + CHR	low	9
second hour	VIR	EXT + CHR	low	–
Immunoglobulin G	CHR	EXT + VIR	high	14
Immunoglobulin A	CHR	EXT + VIR	high	15
Immunoglobulin M	EXT	VIR + CHR	low	5
γ-Globulin	CHR	EXT + VIR	high	13
Aspartate aminotransferase/alanine aminotransferase	CHR	EXT + VIR	high	12
γ-Glutamyltransferase/alkaline phosphatase	CHR	EXT + VIR	high	–
γ-Glutamyltransferase/alanine aminotransferase	VIR	EXT + CHR	low	10
Total bilirubin/γ-glutamyltransferase	VIR	EXT + CHR	high	11
Direct bilirubin/total bilirubin	EXT	VIR + CHR	high	4

The diagnostic power of the indicated analyte in differentiating a "diseased" group (as defined in the second column) from the corresponding complementary group not featuring this disease is analysed by probabilistic test parameters as a function of variable discriminatory cut-off points. The diseased target group may be characterized by either high or low values of the respective analyte. Abbreviations of patient groups: EXT, extrahepatic cholestasis; VIR, acute viral hepatitis; CHR, chronic intrahepatic cholestasis.

Tab. 4. Extrahepatic vs intrahepatic cholestasis (EXT vs VIR + CHR, prevalence 44%)

Analyte	Figure	Discriminator position	*Youden* index	Sensitivity	Specificity	PVpos. (Prev 50%)	PVneg. (Prev 50%)	Overall rating
Alkaline phosphatase	1	400 U/l	38	68	70	64 (69)	74 (69)	useless
		300 U/l	36	95	41	56 (62)	92 (89)	marginal
γ-Glutamyltransferase	2	200 U/l	27	70	57	56 (62)	70 (66)	useless
		100 U/l	19	97	22	50 (55)	90 (88)	marginal
Leucine aminopeptidase	3	60 U/l	33	69	64	60 (66)	73 (67)	useless
Direct bilirubin	4	0.6	19	73	46	46 (57)	72 (62)	useless
/Total bilirubin		0.4	13	100	13	42 (53)	100 (100)	marginal
Immunoglobulin M*	5	2 g/l	32	71	61	59 (65)	73 (68)	useless

* "diseased" patients are represented by low values

Tab. 5. Viral hepatitis vs obstruction and chronic parenchymal liver disease (VIR vs EXT + CHR, prevalence 16%)

Analyte	Figure	Discriminator position	*Youden* index	Sensitivity	Specificity	PVpos. (Prev 50%)	PVneg. (Prev 50%)	Overall rating
Aspartate aminotransferase	6	200 U/l	86	91	95	78 (95)	98 (91)	excellent
		400 U/l	61	61	100	100 (100)	93 (72)	confirms
Alanine aminotransferase	7	300 U/l	90	96	94	76 (94)	99 (96)	excellent
		500 U/l	74	74	100	100 (100)	95 (79)	confirms
		200 U/l	87	100	87	59 (88)	100 (100)	excludes
Lactate dehydrogenase	8	300 U/l	63	83	80	43 (81)	96 (82)	useful
		200 U/l	34	100	34	22 (60)	100 (100)	excludes
Erythrocyte sedimentation rate 1 h*	9	30 mm	54	87	67	33 (73)	96 (84)	useful
		60 mm	38	100	38	23 (62)	100 (100)	excludes
Erythrocyte sedimentation rate 2 h*	—	50 mm	61	78	83	47 (82)	95 (79)	useful
		90 mm	39	100	39	24 (62)	100 (100)	excludes
γ-Glutamyltransferase/alanine aminotransferase*	10	4	57	100	57	30 (70)	100 (100)	excludes
Total bilirubin/γ-glutamyltransferase	11	0.04	41	65	76	34 (73)	92 (68)	excludes

* "diseased" patients are represented by low values

Tab. 6. Chronic parenchymal liver disease vs viral hepatitis and obstruction (CHR vs VIR + EXT, prevalence 40%)

Analyte	Figure	Discriminator position	*Youden* index	Sensitivity	Specificity	PVpos. (Prev 50%)	PVneg. (Prev 50%)	Overall rating
Aspartate aminotransferase/alanine aminotransferase	12	1.0	69	83	86	80 (86)	88 (83)	useful
		1.5	54	57	97	92 (95)	77 (69)	confirms
γ-Globulins	13	20 g/l	45	48	97	90 (94)	74 (65)	confirms
Immunoglobulin G	14	16 g/l	44	64	80	68 (76)	77 (69)	useless
		36 g/l	9	9	100	100 (100)	63 (52)	confirms
Immunoglobulin A	15	5 g/l	44	57	87	74 (81)	76 (67)	useless
		9 g/l	20	20	100	100 (100)	65 (56)	confirms
Cholinesterase*	16	1500 U/l	37	48	89	74 (81)	72 (63)	useless
γ-Glutamyltransferase/alkaline phosphatase	—	1.5	21	26	95	79 (84)	66 (56)	useless

* "diseased" patients are represented by low values

tase, γ-glutamyltransferase (fig. 2) and direct bilirubin/total bilirubin at 300 U/l, 100 U/l, and 0.4, respectively, were used as cut-off points, these analytes did reveal some marginal utility for the exclusion of extrahepatic obstruction (PVneg 92%, 90% and 100%, respectively, when the prevalence of obstruction is 44%; or 89%, 88% and 100%, respectively, for a calculated "standard" prevalence of 50%). The analytes leucine aminopeptidase (fig. 3) and IgM (fig. 5) were of no value in this regard.

Viral hepatitis versus other hepatobiliary diseases

A number of analytes were useful for differentiating between acute viral hepatitis and the remaining three diagnostic categories. At a cut-off point of 200 U/l or 300 U/l, respectively, aspartate aminotransferase and alanine aminotransferase (figs. 6 and 7) were powerful discriminators with very high *Youden* indices well above 80% resulting from sensitivities and specificities of 90% or higher. Values below these cut-off levels reliably excluded acute viral hepatitis (PVneg 98% and 99% respectively, when the prevalence of VIR is 16%, or 91% and 96% for a calculated "standard" prevalence; tab. 5 and fig. 6–7). We also found that lactate dehydrogenase (fig. 8), the ratio of total bilirubin/γ-glutamyltransferase (fig. 11) and γ-glutamyltransferase/alanine aminotransferase (fig. 10) and the erythrocyte sedimentation rate (fig. 9) are useful at certain cut-off points not necessarily coinciding with maximal efficiency. Values below (lactate dehydrogenase, total bilirubin/γ-glutamyltransferase) or above (γ-glutamyltransferase/alanine aminotransferase, erythrocyte sedimentation rate 1 h, erythrocyte sedimentation rate 2 h) these discriminators, as indicated in table 5, made the diagnosis of viral hepatitis very unlikely (PVneg 92% – 100%; prevalence of VIR 16%; see also figs. 6–11).

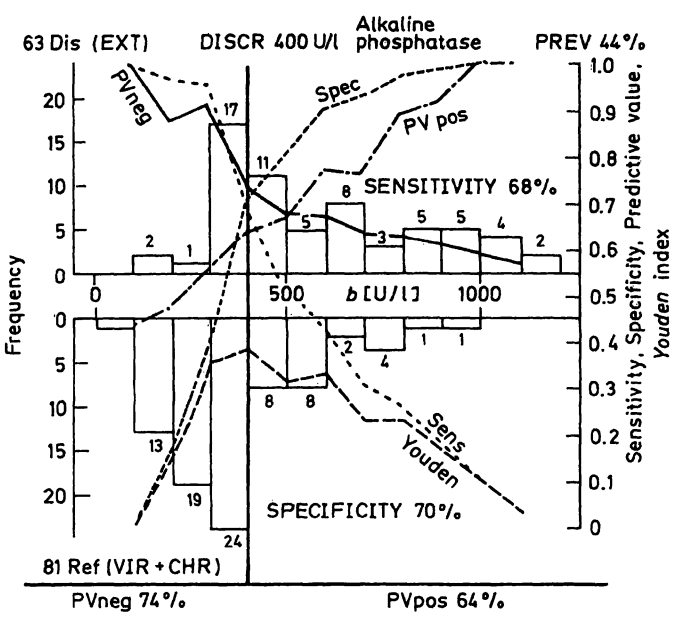

Fig. 1. Double histogram of alkaline phosphatase values in patients with extrahepatic cholestasis (= EXT) ("diseased" (= Dis); n = 63; top of graph) versus intrahepatic cholestasis (viral hepatitis = VIR, chronic parenchymal liver disease = CHR) ("reference" (= Ref); n = 81; bottom of graph). The number of diseased and reference patients for each category of alkaline phosphatase values in U/l is indicated, with alkaline phosphatase missing in 1 patient of the "diseased" group. The graph simultaneously displays sensitivity (sens) (- - - - -), specificity (spec) (-----), *Youden* index (— — — —), the predictive value positive (PVpos) (—·—·—) and the predictive value negative (PVneg) (———) as a function of any randomly selected alkaline phosphatase value serving as discriminator (DISCR). For instance, at a cut-off point of 400 U/l representing the highest *Youden* index, alkaline phosphatase has a sensitivity of 68%, a specificity of 70%, a *Youden* index of 38%, a PVpos of 64% and a PVneg of 74% (or 69% and 69%, respectively, at a computed "standard" disease prevalence (PREV) of 50%) for extrahepatic cholestasis, and thus appears to be useless. In contrast, a cut-off point of 300 U/l, not coinciding with maximal efficiency, is clinically more useful since values below this level indicate absence of disease with a PVneg of 92% (or 89% at a computed "standard" disease prevalence). To calculate "%" the values of the right ordinate must be multiplied by 100.

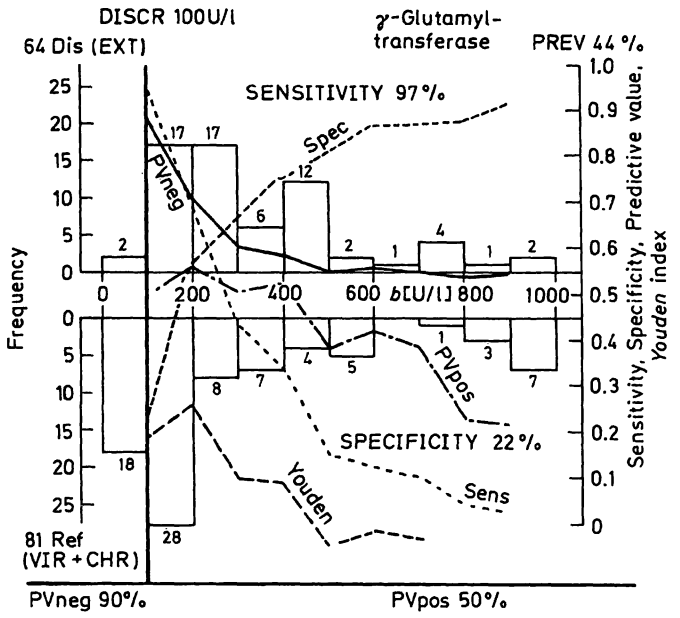

Fig. 2. γ-Glutamyltransferase has a marginal usefulness for excluding extrahepatic cholestasis at values below 100 U/l (PVneg 90%).

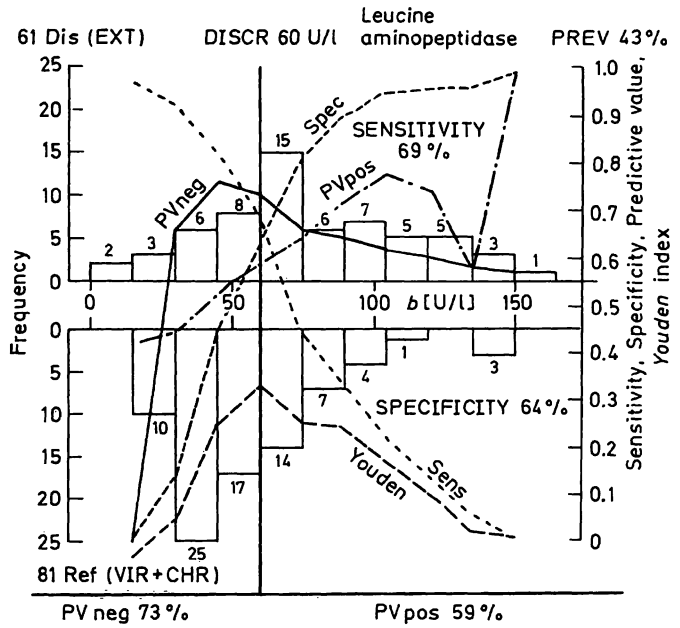

Fig. 3. Leucine aminopeptidase is useless in the differentiation between extrahepatic and intrahepatic cholestasis.

Chronic parenchymal liver disease versus others

For the differentiation between chronic parenchymal liver disease and the three other complementary diagnostic categories, the ratio of aspartate aminotransferase/alanine aminotransferase (fig. 12) and the serum γ-globulin level (fig. 13) were the most useful serological analytes (tab. 6). The *Youden* indices ranged from 45% to 69%. Above a cut-off point of 1.5 and 20 g/l, respectively, the ratio aspartate aminotransferase/alanine aminotransferase and the serum γ-globulin concentrations strongly suggested chronic intrahepatic cholestasis with a PVpos of 92% and 90% for a prevalence of CHR of 40%, or 95% and 94% for a "standard" disease prevalence. There was also a high PVpos for very high values of IgG above 36 g/l and of IgA above 9 g/l (figs. 14–15). However, this was merely of minor diagnostic relevance, since the latter criteria applied to no more than 5 (8.6%) and 11 (19.6%) patients of the CHR category.

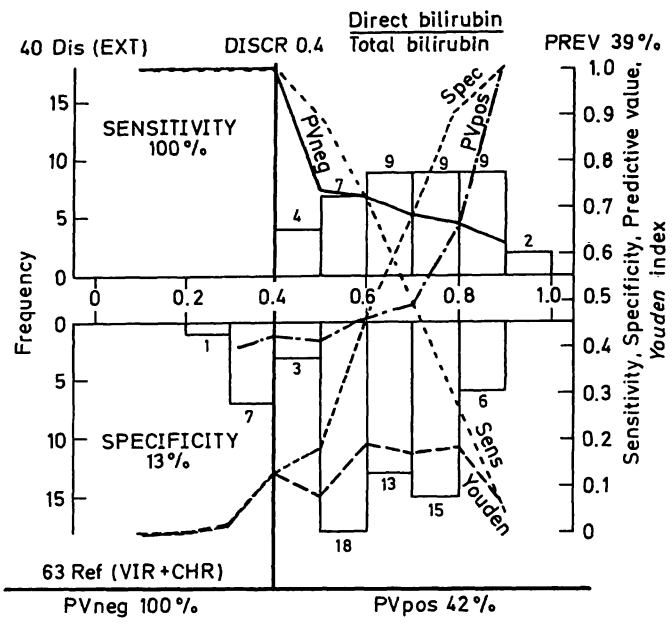

Fig. 4. Double histogram of the ratio of direct and total bilirubin in patients with extrahepatic cholestasis ("diseased"; n = 40; top of graph) versus intrahepatic cholestasis ("reference"; n = 63; bottom of graph). This ratio was computed in patients with elevated total serum bilirubin concentrations only. Computation of this ratio is of no diagnostic use, except for values below a cut-off point of 0.4 (PVneg 100%; see also tab. 4 and legend to fig. 1).

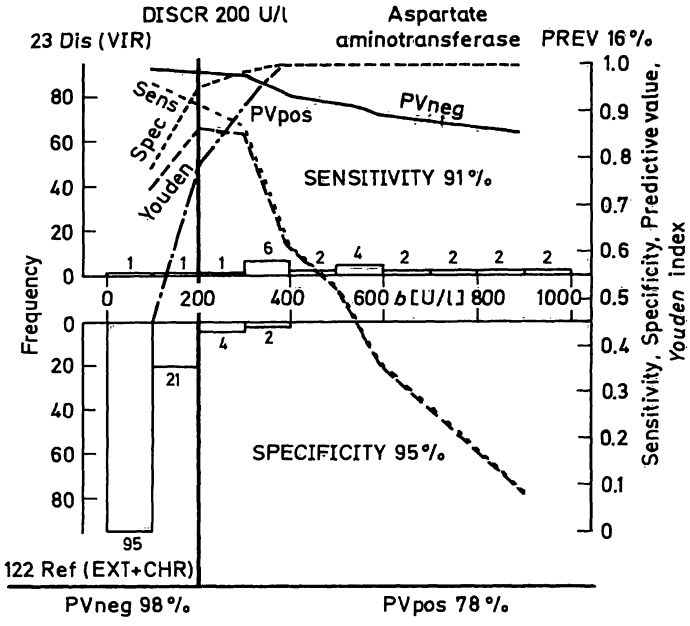

Fig. 6. At a cut-off point of 200 U/l, aspartate aminotransferase is a powerful disciminator between viral hepatitis and the other forms of hepatobiliary diseases (for further explanations, see also legend to fig. 7).

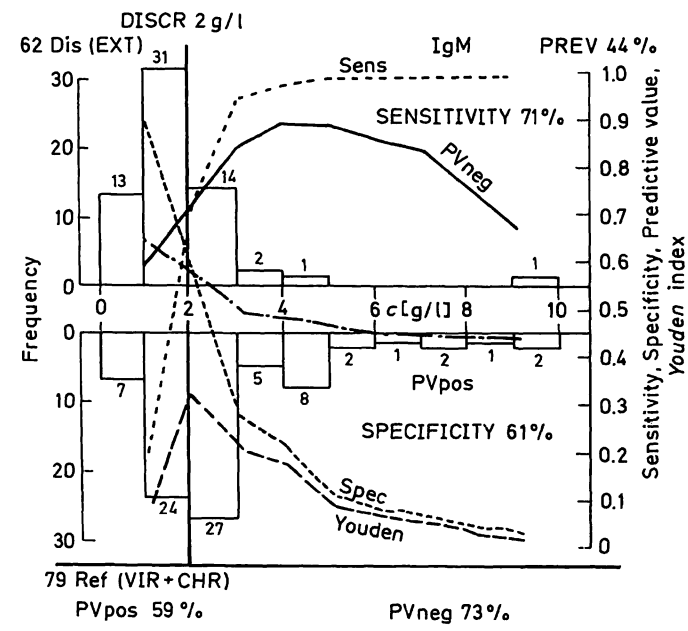

Fig. 5. Immunoglobulin M is useless in the differentiation between extrahepatic and intrahepatic cholestasis. Disease (extrahepatic obstruction) is represented by low values of this analyte.

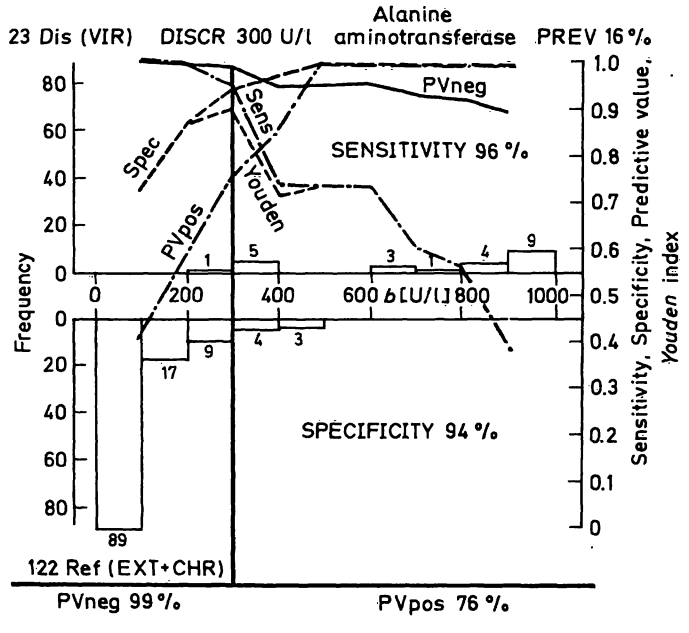

Fig. 7. Double histogram of alanine aminotransferase values in U/l in patients with viral hepatitis ("diseased"; n = 23; top of graph) versus all other diagnostic groups ("reference"; n = 122; bottom of graph). At a cut-off point of 300 U/l, this analyte possesses high diagnostic power: sensitivity 96%, specificity 94%, PVpos 76%, PVneg 99% (or 94% and 96%, respectively, at a "standard" disease prevalence of 50%).

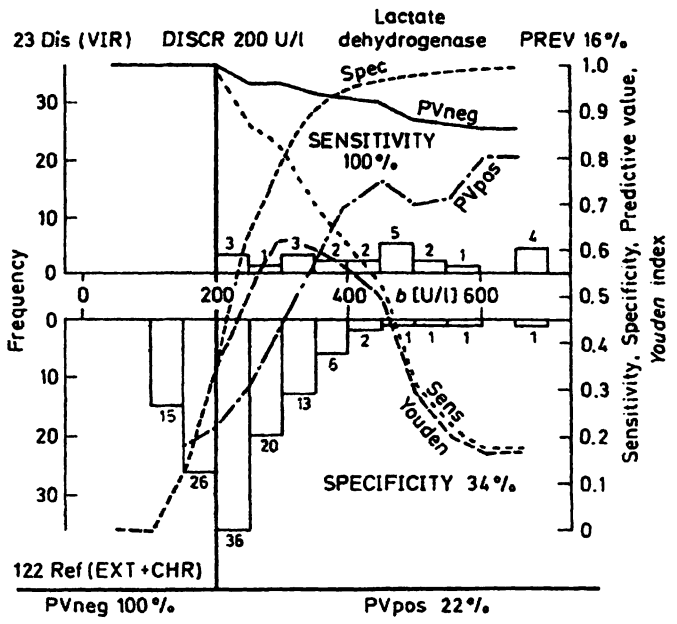

Fig. 8. Lactate dehydrogenase has marginal usefulness for excluding viral hepatitis at values below 200 U/l (PVneg 100%).

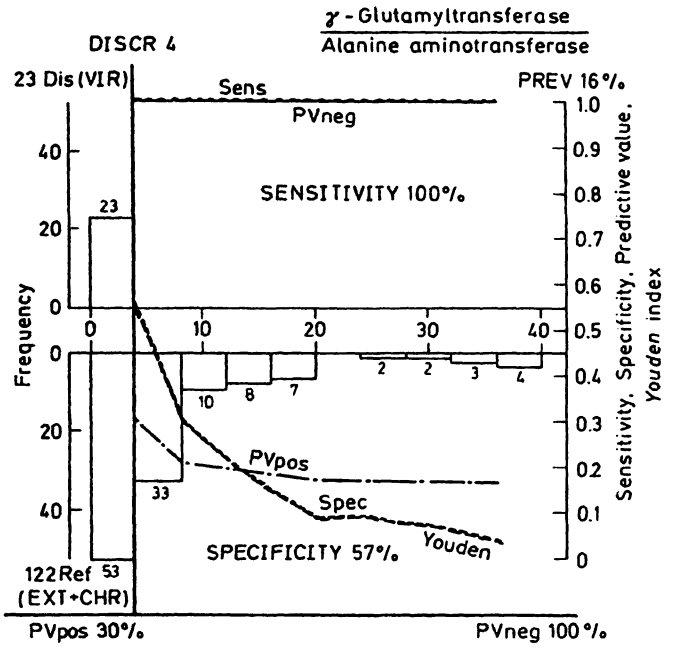

Fig. 10. The ratio γ-glutamyltransferase/alanine aminotransferase has marginal usefulness for excluding viral hepatitis at values above 4. Note, that disease (viral hepatitis) is represented by a low ratio of these analytes.

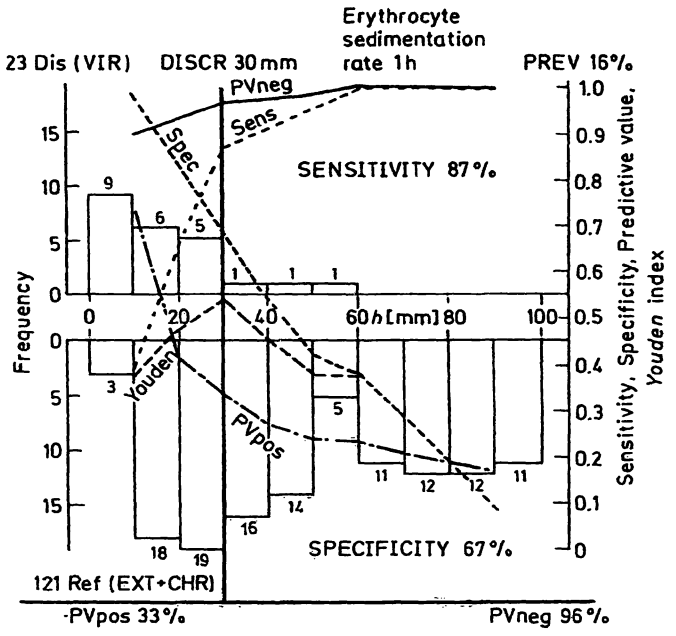

Fig. 9. Double histogram of erythrocyte sedimentation rate in mm in the first hour in patients with acute intrahepatic cholestasis ("diseased"; n = 23; top of graph) versus all other diagnostic groups ("reference"; n = 121; bottom of graph, one value missing in this group). At a cut-off point above 30 mm, this analyte makes the diagnosis of acute intrahepatic cholestasis very unlikely (PVneg 96%, albeit only 84% at a "standard" disease prevalence). Note that the "diseased" group is represented by low values for this analyte.

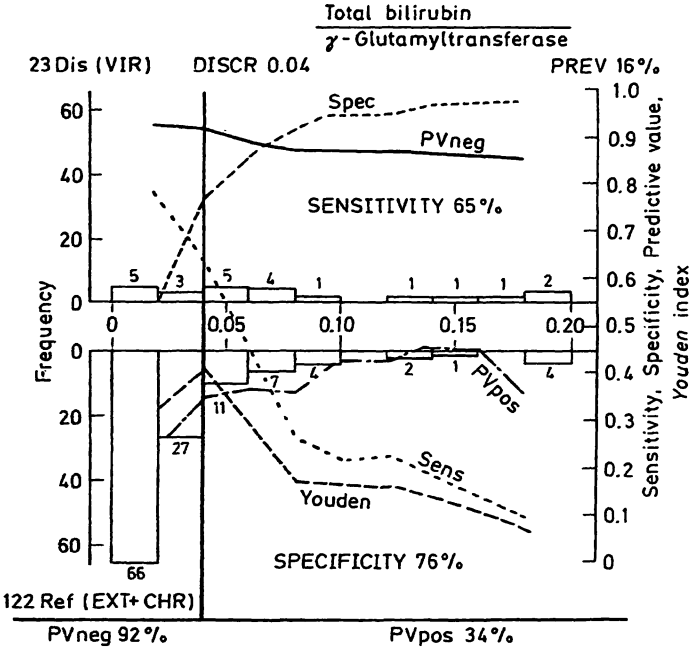

Fig. 11. The ratio total bilirubin/γ-glutamyltransferase has marginal usefulness for excluding viral hepatitis at values below 0.04 (PVneg. 92%).

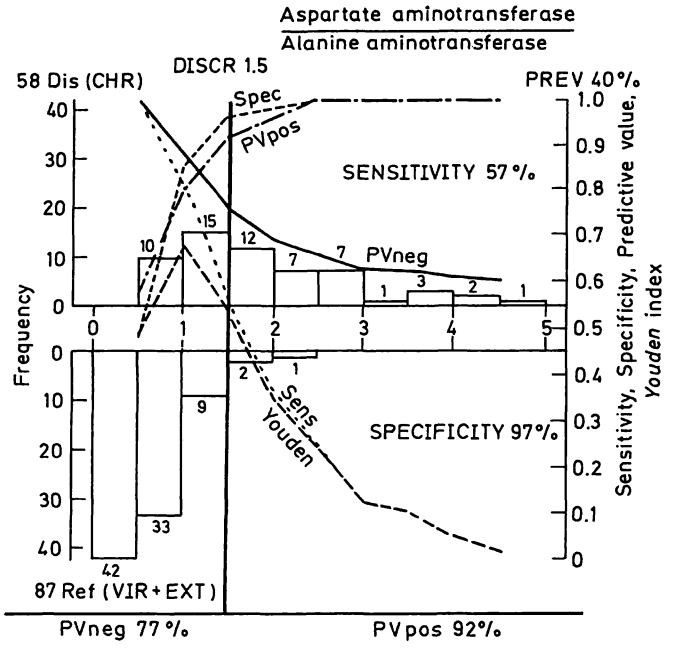

Fig. 12. At aspartate aminotransferase/alanine aminotransferase ratios above 1.5, this quotient is useful for confirming chronic parenchymal liver disease (PVpos 92%).

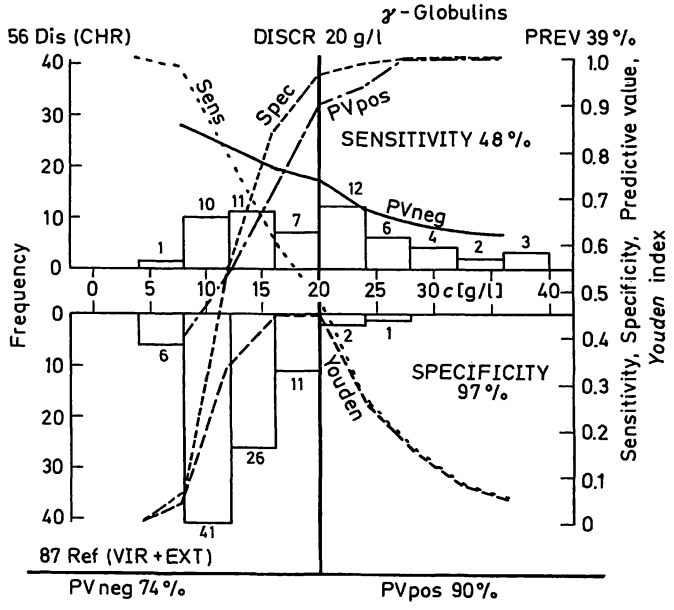

Fig. 13. Serum γ-globulin concentrations above 20 g/l confirm chronic parenchymal liver disease (PVpos 90%).

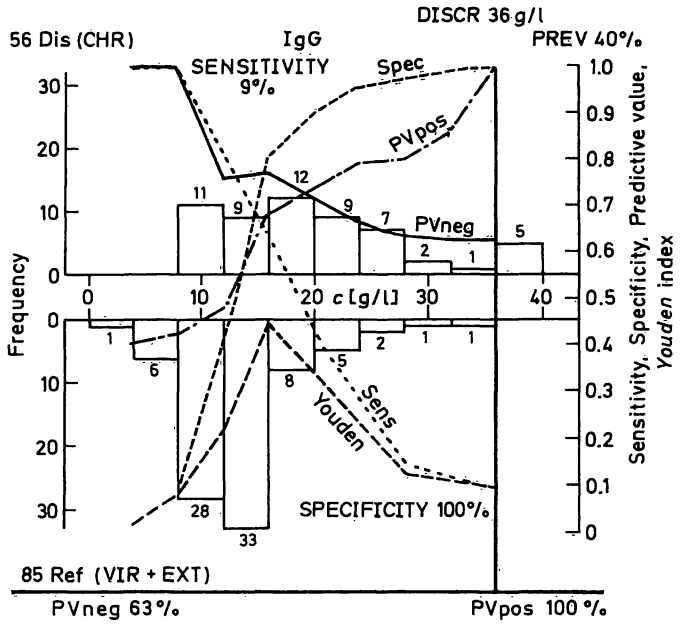

Fig. 14. Serum immunoglobulin G concentrations above 36 g/l confirm chronic parenchymal liver disease (PVpos 100%). The clinical usefulness is marginal, considering a sensitivity 9%.

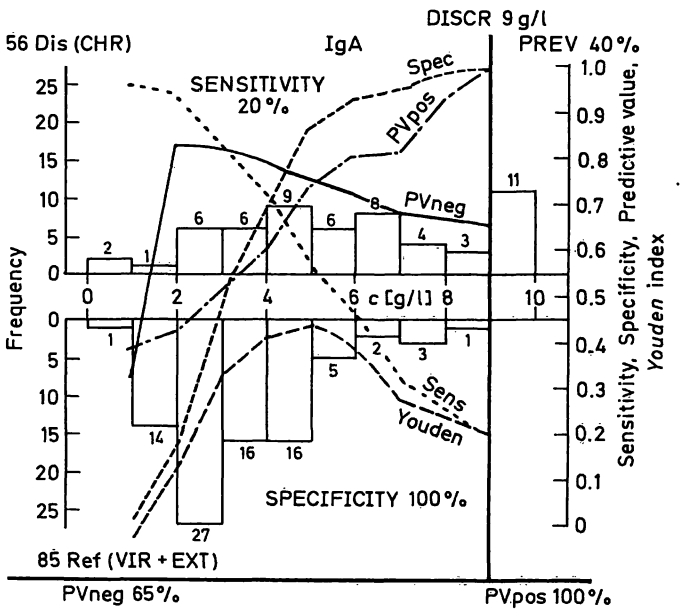

Fig. 15. Serum immunoglobulin A concentations above 9 g/l confirm chronic parenchymal liver disease (PVpos 100%). The clinical usefulness is limited, considering a sensitivity of 20%.

Discussion

The rate of morphological diagnostic proof obtained in this study (72%) corresponds to other clinical investigations of cholestatic patients (e. g. 71% in the study of *Malchow-Moller* (4)). It has to be kept in mind that the patients described here were selected for cholestasis, as indicated by elevated serum levels of alkaline phosphatase and/or γ-glutamyltransferase and/or bilirubin. Therefore, data for the diagnostic groups with viral hepatitis (VIR) and with chronic parenchymal liver disease (CHR) will primarily apply to those disease subgroups with more obvious cholestatic features. With regard to the evaluation of diagnostic tests in cholestasis, this fact may place an

even higher demand on their discriminatory power, thus adding to rather than subtracting from the validity of the results reported here.

In addition to the well defined reference groups listed in table 3, a number of other less prevalent disease states possibly associated with cholestasis and not included in this study have to be considered. However, many of these less frequent diagnoses, like liver metastases or ischaemic liver failure due to cardiac insufficiency, are either readily diagnosed by ultrasonography or are readily suggested by the clinical setting in which they occur. Thus they rarely cause much diagnostic uncertainty. Nevertheless, the specificity given in tables 4 to 6 is the specificity against the background of those well defined, homogeneous diseases making up the respective reference groups of this study; the various further less prevalent diseases, which may also present with cholestatic features, have not been taken into consideration.

Extrahepatic versus intrahepatic cholestasis

The graphical analyses presented here clearly confirm that laboratory analytes like alkaline phosphatase, γ-glutamyltransferase, leucine aminopeptidase and IgM are of little help in the basic differentiation between extrahepatic cholestasis and bile secretory failure due to parenchymal liver disease (1, 5), when maximum efficiency is selected as discriminator for a 2 × 2 table analysis.

This lack of useful discriminatory power also applies to the ratio direct bilirubin/total bilirubin, as determined by the conventional diazo method (6). High performance liquid chromatography (HPLC) after alkaline methanolysis has recently been introduced as a specific method for estimating conjugated bilirubin (7). Demonstration of esterified bilirubins in plasma by this reaction appears to evolve as the single most sensitive marker of hepatobiliary disease and may serve to exclude *Gilbert*'s syndrome by the detection of appreciable amounts of such esters (7), but it likewise does not discriminate between extrahepatic or intrahepatic variants of cholestatic disease. This differentiation clearly is a domain of the imaging techniques, especially ultrasonography.

The graphical display did reveal the clinical usefulness of alkaline phosphatase (cut-off point 300 U/l; PVneg 92%, "standard" PVneg 89%; fig. 1), γ-glutamyltransferase (cut-off point 100 U/l; fig. 2) and direct bilirubin/total bilirubin (cut-off point 0.4; fig. 4, tab. 4) for excluding extrahepatic obstruction in the reference groups. The double histograms thus show that the clinically most meaningful discriminator position does not necessarily coincide with that giving the highest *Youden* index, or maximum "efficiency". No single cut-off point is appropriate for every diagnostic demand. Discriminator positions rather have to be tailored to satisfy specific needs, be it a search for high positive or negative predictive values or maximal efficiency. The optimal discriminator position for any such diagnostic purpose can be easily gleaned from the double histogram display of the computer graphs. Such plots thus help to utilize the diagnostic potential of the diagnostic variables to a fuller extent.

Viral hepatitis versus other hepatobiliary diseases

On the contrary, the serum aminotransferases aspartate aminotransferase and alanine aminotransferase (figs. 6–7) are excellent criteria for the diagnosis of acute viral hepatitis even at their maximal efficiency value. At a cut-off point of 200 U/l and 300 U/l, respectively, they had *Youden* indices well above 80%, with sensitivity and specificity rates of 90% or higher, while negative predictive values of 98% and 99% or 91% and 96% at standard prevalence rates, respectively, reliably excluded this diagnosis for values below these discriminators (tab. 5). Like previous investigators (1), we did not observe aminotransferases above 500 U/l in the reference groups, thereby raising the PVpos and the specificity at this cut-off point to 100% (figs. 6–7). However, the inclusion of other reference groups such as hepatic ischaemia (8) would appreciably subtract from the specificity associated with this choice of discriminator position.

In addition to the aminotransferases, lactate dehydrogenase and erythrocyte sedimentation rate were of relevance for excluding the diagnosis of acute viral hepatitis at specific cut-off points (figs 8–9). This role of lactate dehydrogenase and erythrocyte sedimentation rate was previously not fully appreciated. With erythrocyte sedimentation rate 1 h and erythrocyte sedimentation rate 2 h, "diseased" patients with viral hepatitis are characterized by low rather than high values of these variables. Therefore, sensitivity and PVneg increase with higher values and specificity and PVpos decrease (fig. 9), which is a reverse of the situation where "disease" is characterized by high values, e. g. of aspartate aminotransferase or alanine aminotransferase (figs. 6–7).

Chronic parenchymal liver disease versus others

Further analyses showed that high serum γ-globulin levels were helpful for the identification of chronic

intrahepatic cholestasis (PVpos 90% at a discriminator position of 20 g/l, given a prevalence for CHR of 40%: fig. 13). IgG and IgA had little and cholinesterase no value in this regard (tab. 6; figs 14–16).

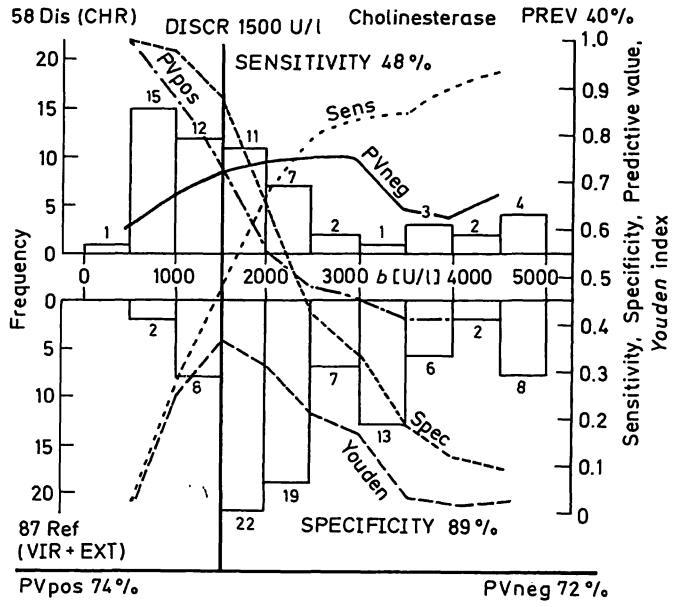

Fig. 16. Lack of usefulness of cholinesterase for the differentiation of chronic parenchymal liver disease versus other disease categories.

Further analytes and ratios

We also investigated several other diagnostic ratios in addition to direct bilirubin/total bilirubin (fig. 4). The ratio γ-glutamyltransferase/alanine aminotransferase as described by *Schmidt & Schmidt* (1) was a useful diagnostic parameter for acute viral hepatitis with a *Youden* index of 57% and a PVneg of 100% at a cut-off point of 4 (tab. 5; fig. 10). As with erythrocyte sedimentation rate, "disease" is characterized by low values of this index. The ratio total bilirubin/γ-glutamyltransferase as defined by *Poynard* et al. (9) is a prognostic indicant in cirrhotic patients, high values being associated with reduced survival. As indicated in table 5, this ratio may also be used to make a diagnosis of acute viral hepatitis unlikely (PVneg 92% at a cut-off point of 0.04: fig. 11). However, the apparent usefulness of this ratio probably depends to some extent on a selection of patients with more obvious cholestatic features in this series.

The best known ratio is *De Ritis'* aspartate aminotransferase/alanine aminotransferase, which has been found to be elevated in patients with alcoholic hepatitis and cirrhosis (> 2, l.c. (10, 11)), postnecrotic cirrhosis (1.74), chronic hepatitis (1.3), but not obstructive jaundice (0.81) and viral hepatitis (0.74, l.c. (10)). It has also been successfully used to differentiate intrahepatic cholestasis from extrahepatic obstruction in chronic alcoholic pancreatitis (12). This ratio likewise proved useful in the present study for the identification of chronic intrahepatic cholestasis. The cut-off point giving the highest efficiency was 1.0. However, neither predictive value reached the 90% limit at this level, making a cut-off point of 1.5 more meaningful for individual diagnostic decisions (tab. 6; fig. 12). The γ-glutamyltransferase/alkaline phosphatase ratio (11) was useless in this regard (tab. 6).

Conclusions

Computer-assisted graphical analyses shed some additional light on the discriminatory power of conventional laboratory analytes for the differentiation between extrahepatic cholestasis and cholestasis due to acute or chronic parenchymal liver disease. Our observations confirm that aminotransferase levels are excellent criteria for the diagnosis of acute viral hepatitis; to a lesser extent, this is also true for serum γ-globulin concentrations and the *De Ritis* quotient with regard to intrahepatic cholestasis due to chronic parenchymal liver disease. The analyses also point to the additional, less appreciated value of lactate dehydrogenase, erythrocyte sedimentation rate and especially of the ratio γ-glutamyltransferase/alanine aminotransferase for the probabilistic exclusion of acute viral hepatitis.

These graphical analyses by no means abolish uncertainties in individual diagnostic decisions. They rather allow a precise estimate of positive or negative likelihoods in these cases and thus help to clearly define the magnitude of that uncertainty. Above all, they readily and comprehensively display the entire distribution of laboratory data in "disease" and reference states and thus enable a more flexible usage and a fuller exploitation of their true diagnostic potential.

References

1. Schmidt, E. & Schmidt, F. W. (1984) Dtsch. Med. Wochenschr. *109*, 139–144.
2. Gerhardt, W. & Keller, H. (1986) Scand. J. Clin. Lab. Invest. *46* Suppl. *181*, 1–75.
3. Börsch, G., Wegener, M., Schmidt, G., Coenen, C. & Glocke, M. (1986) Med. Klin. *81*, 738–744.
4. Malchow-Moller, A., Thomsen, C., Hilden, J., Matzen, P., Mindeholm, L., Juhl, E. & the Copenhagen Computer Icterus Group (1985) Scand. J. Gastroenterol. *20*, 155–162.
5. Penn, R. & Worthington, D. J. (1983) Brit. Med. J. *286*, 531–535.
6. Müller-Lissner, S. A., Presch, A., König, A., Sonnenberg, A. & Horn, K. (1984) Dtsch. Med. Wochenschr. *109*, 576–580.
7. Fevery, J. & Blanckaert, N. (1986) J. Hepatol. *2*, 113–121.
8. Wegener, M., Börsch, G., Reitemeyer, E. & Schmidt, G. (1986) Med. Klin. *81*, 832–835.
9. Poynard, T., Zourabichvili, O., Hilpert, G., Naveau, S., Poitrine, A., Benatar, C. & Chaput, J. C. (1984) Hepatology *4*, 324–327.
10. Cohen, J. A. & Kaplan, M. M. (1979) Dig. Dis. Sci. *24*, 835–838.
11. Spech, H. J. & Liehr, H. (1983) Z. Gastroenterol. *21*, 89–96.
12. Buehler, H., Muench, R., Schmid, M. & Ammann, R. (1985) Scand. J. Gastroenterol. *20*, 851–856.

Priv.-Doz. Dr. G. Börsch
Department of Medicine
St. Josef-Hospital
Gudrunstr. 56
D-4630 Bochum